tribute

In Memoriam: Lina M. Obeid (1957–2019)

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On November 29, 2019 the world lost a remarkable woman, Lina M Obeid, MD. Lina was a wife, mother, grandmother, sister, daughter, friend, colleague, mentor, and internationally-renowned physician scientist. Lina's research, which spanned more than 30 years, was pivotal in the fields of sphingolipid metabolism, apoptosis, and most recently, cancer. Her career was marked by seminal and field-changing scientific discoveries, training and mentoring of graduate students and postdoctoral fellows, and service to the veteran population as a physician scientist.

Lina Marie Obeid was born on July 22, 1957, in New York City to Sami and Rosette Obeid. She grew up in Beirut, Lebanon, and learned a love for medicine and research from her father, a physician, at a young age. She attended Rutgers University in New Jersey, where she earned a bachelor's degree in Chemistry, and then returned to Lebanon, where she earned an MD with distinction from the American University of Beirut in 1983. She moved to Duke University for her internship and residency in internal medicine, followed by a fellowship in endocrinology and geriatrics. Her work in the laboratory of Nobel Laureate Dr. Robert J. Lefkowitz at Duke sparked her interest in the varied roles of signaling lipids in cell stress and implications for disease. She joined the faculty at Duke in 1992 in the Departments of Medicine and Cell Biology and in 1996 was promoted to Associate Professor of Medicine, shortly after obtaining a First Award from the National Institute of Aging. In 1998, she moved to the Medical University of South Carolina as a Boyle Professor of Medicine in the Division of Geriatrics and Professor of Biochemistry and Molecular Biology. During her time in Charleston, Lina was funded by the Department of Veteran's Affairs and practiced medicine at the Ralph H. Johnson VA Medical Center. In 2012, Lina was recruited to Stony Brook University as the Dean for Research and Professor of Medicine. Lina maintained continuous National Institutes of Health and Department of Veteran's Affairs funding for more than 25 years.

Photo credit: John Griffin/Stony Brook University

Throughout her academic career, Lina published more than 200 peer-reviewed publications and over 50 reviews and book chapters. Lina's 1993 *Science* manuscript was the first report of a role for the bioactive lipid ceramide in apoptotic cell death. She continued work on this topic throughout her career, including cloning many of the major enzymes of sphingolipid metabolism in *Saccharomyces cerevisiae*, which facilitated the identification of their mammalian homologs. Subsequent work described sphingolipids and their roles in cell death mediated by a host of insults, including cancer chemotherapeutic agents.

Lina also worked extensively in aging and cellular senescence. Her laboratory determined that diacylglycerol levels were decreased in senescent cells and that this was due to low activity of phospholipase D. This low-level activity was due in part to increases in ceramide in aging cells. She went on to link increased levels of ceramide with growth arrest and cell senescence. She defined the mechanism of this growth arrest at the molecular level and showed that

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ceramide inhibited cell cycle progression and telomerase activity in cells, thus turning on a biochemical program of cell senescence. These observations opened up a new field of study on the role of ceramides in cellular senescence, cell cycle arrest and aging biology.

Lina's work in ceramide synthases (CerSs) spanned her career. Her laboratory first demonstrated that a critical domain (the LAG domain) was required for CerS activity in cells, and that these enzymes were differentially regulated by chemotherapeutic agents. Moreover, she illustrated that their differential regulation led to different ceramide species being generated in apoptosis, ER stress, and autophagy. Her laboratory also discovered that CerSs were regulated by the pro-apoptotic protein BAK such that BAK was required for CerS activity in cells and in vitro. Recent work in her laboratory, published in *Cell Metabolism* in 2017, defined a novel interaction between DGAT2 and CerS that led to the sequestration of ceramides as acylceramides thereby protecting cells from apoptosis. These studies began to define specific ceramide species in different cell regulatory pathways and allowed the novel concept of "many ceramides."

Much of Lina's academic career focused on the actions of sphingosine kinases (SKs) and their bioactive lipid product, sphingosine-1-phosphate (S1P). Her laboratory cloned the human SK1 and studied its regulation in cells and in knockout mice, and she was the first to demonstrate the role for SK1 in cancer. Very early on, she found that the enzyme was activated by translocation to the plasma membrane in response to phorbol esters. She subsequently showed that the enzyme was overexpressed in many cancers and upregulated in hypoxia. In addition, studies from her laboratory showed that increases in cellular levels of SK1 led to increased secretion of S1P, and that these changes were associated with increased angiogenesis and lymphangiogenesis. Her most recent work uncovered a critical role of SK1 in mediating p53 null cancers, whereby her lab determined that SK1 was proteolyzed upon p53 activation and that loss of p53 led to a dysregulated SK1/S1P pathway that, in part, drove thymic lymphomas and other cancers in p53 null mice. Her lab also implicated SK1 in several mouse models of cancer. Her publications in *FASEB Journal* in 2009 demonstrated that the SK1/S1P pathway was critical for mediating TNF's inflammatory responses and activation of the COX-2/PGE2 pathway in cells and in animal models of colitis and colitis associated cancer (and arthritis).

Dr. Obeid's abundant seminal contributions to science were honored in 2019 with the Lifetime Achievement Award from the Eicosanoid Research Foundation, which was awarded jointly with Dr. Yusuf Hannun. This was the first joint award ever given and, more importantly, Lina was the first woman to receive the award.

Lina, a true bon vivant, brought life and sparkle to every gathering. Her love for science was only equaled by her passion for her family and for enjoying her life. She was an enthusiastic traveler, dancer, and gourmet chef. Together with her husband and true life partner, Yusuf Hannun, Lina raised three remarkable children who now embody her intelligence, sophistication, personal warmth, kindness, and empathy. She was extremely proud of her children and their outstanding accomplishments. She loved watching the triplets grow into their own and loved traveling with and through them as they experienced the world. Perhaps the pinnacle(s) of her excitement occurred with the birth of her grandchildren, Evelyn and Yusuf. Lina loved food; to cook it, to eat it and to share it with others. Her travels were planned (when they didn't include a scientific meeting and even sometimes when they did) around visiting family and friends and exploring different places, cultures, and cuisines. Her effervescence was perhaps most evident when she was dancing by herself, with Yusuf, or with friends and often to the beat of her own drummer. She was remarkable, brilliant, elegant, and truly special.

Lina directly mentored more than a dozen graduate students, seven of whom were MSTP MD/PhD students; passing on her wisdom as a true physician scientist. She mentored more than 30 postdoctoral fellows and junior faculty in their careers and interests. Most remarkable about this number is that more than 2/3rds of her mentees were women. She had a true talent for empowering women and focused not only on her mentees' scientific development and success, but also on their personal lives, supporting them as they got engaged and married, encouraging many to start families, or to add an extra week to their vacation to explore and relax. In short, Lina taught those around her to pursue their own dreams professionally and personally, offering abundant personal support, advice, and encouragement. Lina mentored many, many other scientists who never picked up a pipette in her lab through several means, including the SC COBRE in Lipidomics and Pathobiology at the Medical University of South Carolina, as the CoDirector of the MTSP program in Charleston, as the Dean for Research at Stony Brook University, and through countless interactions at many meetings. In fact, as the director of the COBRE program, she played a key role in shaping the sphingolipid field through the selection and mentorship of junior faculty in sphingolipid research. As a mentor, Lina demonstrated a level of warmth, openness, and generosity of spirit that is rarely encountered. She inspired mentees with her enthusiasm and creativity, always seeing possibilities for their research and their success. She managed to do all these things with an unending positive attitude, extraordinary grace, and the warmest of smiles.

Lina once said that the only time she was ever nervous was when she introduced guest speakers, because she always wanted to be sure to emphasize the points and achievements they would want the audience to know. We have done our best to do just that for Lina. There are no words to adequately describe Lina—she was a force and she left so much of her essence in so many of us.